Brief Summary of the Circulatory System Devices Panel Meeting – June 13, 2012

Introduction:

The Circulatory System Devices Panel of the Medical Devices Advisory Committee to the Food and Drug Administration met on June 13, 2012 to make recommendations and vote on information related to the PMA P110021 for the Edwards SAPIEN Transcatheter Heart Valve sponsored by Edwards Lifesciences. This is a first-of-a-kind transcatheter aortic heart valve for patients who are at high (greater than or equal to 15%) risk for mortality from surgical aortic valve replacement. The Edwards SAPIEN Transcatheter Heart Valve, model 9000TFX, sizes 23mm and 26mm and accessories have been reviewed by the Division of Cardiovascular Devices within the Center for Devices and Radiological Health of the Food and Drug Administration under Premarket Approval (PMA) application P110021, which is the subject of this Advisory Panel meeting. This device was previously reviewed by FDA for inoperable patients and was approved for this specific patient population on November 2, 2011.

The company has proposed the following Indications for Use:

Transfemoral Procedure

The Edwards SAPIEN Transcatheter Heart Valve, model 9000TFX, sizes 23 mm and 26 mm, is indicated for patients with severe symptomatic native aortic valve stenosis who have been examined by a heart team including a cardiac surgeon and found to be:

- inoperable and in whom existing co-morbidities would not preclude the expected benefit from correction of the aortic stenosis, or

- operable candidates for aortic valve replacement but who are at a greater than or equal to high (a greater than or equal to 15%) risk of mortality for surgical aortic valve replacement.

The RetroFlex Balloon Catheter is indicated for valvuloplasty of a stenotic cardiac valve prior to implantation of the Edwards SAPIEN transcatheter heart valve.

The RetroFlex 3 Delivery System is indicated for the transfemoral delivery of the Edwards SAPIEN Transcatheter Heart Valve.

The Crimper is indicated for use in preparing the Edwards SAPIEN Transcatheter Heart Valve for implantation.

Transapical Procedure

The Edwards SAPIEN Transcatheter Heart Valve, Model 9000TFX, sizes 23 mm and 26 mm, is indicated for transapical delivery in patients with severe symptomatic native aortic valve stenosis who have been examined by a heart team including a cardiac surgeon and found to be operative candidates for aortic valve

replacement but who are at high (a greater than or equal to 15%) risk of mortality for surgical aortic valve replacement.

The Ascendra Balloon Aortic Valvuloplasty Catheter is indicated for valvuloplasty of a stenotic native aortic valve prior to implantation of the Edwards SAPIEN transcatheter heart valve.

The Ascendra Balloon Catheter is indicated for the transapical delivery of the Edwards SAPIEN Transcatheter Heart Valve.

The Ascendra Introducer Sheath Set is indicated for the introduction and removal of interventional devices used with the Edwards SAPIEN Transcatheter Heart Valve.
The Crimper is indicated for use in preparing the Edwards SAPIEN Transcatheter Heart Valve for implantation.

Panel Deliberations/FDA Questions:

The panel discussed the safety of the device and agreed that:

- Non-disabling strokes were possibly missed, but disabling strokes were not. In the future, they should consider a neurologist as part of the team treating the patient.

- There was not a rigorous anti-thrombotic regimen and what regimens are appropriate in this patient population is not well understood. A specific protocol is necessary.

- Understanding stroke etiology is important, more sophisticated imaging before/after procedure may be helpful, and atrial fibrillation should be studied to determine its association with stroke rate.

- The stroke rate appeared to decrease in Continued Access Protocol (CAP, a non-randomized cohort) patients (as compared to patients enrolled in the pivotal trial cohort), but more information is needed, especially for severe strokes. There are multiple reasons for why the rate could be lower and a PAS or registry data could provide more information.

- Aortic insufficiency results are a concern especially if the valve is used in different populations that might have a longer life expectancy; more information needs to be obtained from a larger sample size. Only two sizes have been studied; additional sizes that are a better physiological match may improve the regurgitation rates. Variables such as each individual patient, physician, and/or device may have played a role.

- The rate of vascular complications seemed to have been lowered in the CAP patients. Many factors might have played a role, such as introduction of the transapical approach, improvements in the delivery system and closure methods, more rigorous screening, and learning curve issues.

The panel discussed the trial conduct issues and their potential impact on interpretation of the data. Acknowledging the difficulties in conducting the trial in a high-risk patient population, the panel agreed that the issues noted have not impacted interpretation of the data in a negative way because assessment of both the Intent-to-Treat (ITT) and As-Treated (AT) populations as well as worst-case sensitivity analyses demonstrated robustness of the results.

The panel also discussed the safety and effectiveness results for the transapical approach and was concerned with the stroke rate. A number of things have changed, such as technology, learning, procedures, etc. As the study stands, it is hard to control for variance between sites to examine this. A larger sample size will be needed to address this.

For the proposed indications for use, the panel discussed the following issues:

- It is important that a cardiac surgeon is involved and that the patient meets with both the surgeon and the cardiologist.
- Consider including the risk score to ensure that the appropriate patients are treated.
- Risk should be defined as being "greater than," rather than "greater than or equal to" 15%.
- The definition of "severe" used to define aortic stenosis should be clarified.
- Consider including New York Heart Association functional classification for heart failure to better define the patients.
- It is important to adhere to the criteria that were used in the trial, such as stipulating valve area, gradient, STS score of >8, assessed operable risk > 15%, and echocardiography criteria.
- It is possible that many of these criteria should be listed in the labeling, and not necessarily in the indications for use.

The panel discussed the gender differences and believed that this *post hoc* analysis is hypothesis generating and the issue should be studied further in future post-approval studies, other trials of similar technology, and further investigation of the CAP data to better understand it. The panel also expressed the need for covariates and propensity scores in the *post hoc* data. The post approval studies (PAS) should pre-specify gender analyses.

Regarding the long term durability, the panel believed that the two- and three-year data seemed reassuring and promising; however, they would like to see 5 year data to address this issue. Also, it is important to report echocardiography data for not only aortic stenosis but also aortic regurgitation in the PAS.

In discussions of the valve-in-valve technique, the panel agreed that there is not enough information available and it should not be endorsed. The labeling can state that the technique has not been studied for safety and effectiveness. The panel also agreed that "bailout," or acute valve-in-valve (i.e., SAPIEN in SAPIEN) use, will be captured in the PAS study and use of valve-in-valve for aortic valve redo surgery (where the patient has already had prior valve replacement and the native valve is not in place) should be a separate study.

The panel discussed the need for a more detailed informed consent and expressed mixed opinions. One opinion stated that surgical aortic valve replacement is the gold standard and the patients need to know the risks associated with the transcatheter aortic valve replacement as an alternative therapy to open heart surgery. The other opinion stated that the risks should be explained in detail to the patients; however, this should be a discussion between the patients and their doctors, and it should not necessarily be the responsibility of the FDA to require a detailed informed consent. The panel also urged the sponsor, the professional medical societies, and the patient advocacy groups to work on creative ways to better educate the patients.

The panel weighed in on the overall safety and effectiveness and believed that the data demonstrate a reasonable assurance of safety and effectiveness, with a number of caveats, such as stroke (especially in the

transapical population), aortic regurgitation, and gender differences. Close monitoring of these issues is needed in the post approval studies.

The panel discussed whether or not the relationship between mortality and aortic regurgitation severity (no/trace versus mild/moderate/severe) within TAVR patients should be monitored in the PAS and agreed that it should, with the stipulation that mild regurgitation should be analyzed separately from moderate and severe regurgitation.

The panel believed that the PAS should be used to monitor short-term and long-term effects of safety and effectiveness of valve-in-valve implantation and that the following endpoints should be incorporated in the PAS:

- More patient centric measures
- Quality of life (QoL)
- Greater detail on atrial fibrillation, aortic regurgitation (no/trace, mild, moderate/severe), and vascular complications
- Duration of hospital stay
- Cause of death
- Serial echocardiography for durability
- Gender analysis
- More detail on types of stroke
- Small subset for imaging on stroke patients
- Subset with implantable loop recorders to understand AF correlation

The panel believed that the labelling should also include information on:

- Gender difference
- Transapical and transfemoral data
- Stroke
- Aortic regurgitation

Vote:

The panel voted on the safety, effectiveness, and risk benefit ratio of the Edwards SAPIEN™ Transcatheter Heart Valve.

Question 1

The panel voted 10-2 that the data shows reasonable assurance that the Edwards SAPIEN™ Transcatheter Heart Valve is safe for use in patients who meet the criteria specified in the proposed indication.

Question 2

The panel voted 12-0 that there is reasonable assurance that the Edwards SAPIEN™ Transcatheter Heart Valve is effective for use in patients who meet the criteria specified in the proposed indication.

Question 3

The panel voted 11-0 (with one abstention) that the benefits of the Edwards SAPIEN™ Transcatheter Heart Valve do outweigh the risks for use in patients who meet the criteria specified in the proposed indication.

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